(19) Japan Patent Office (JP)

(12) Public Patent Disclosure Bulletin (A)

(11) Public Patent Disclosure Bulletin No.

Patent Disclosure 2000-143510
(P2000-143510A)
(43) Date of Publication: May 23, 2000

(51) Int. Cl.[7]	ID Code	FI			Theme code (reference)
A61K 31/404		A61K	31/40	607	4C086
A61P 29/00			31/00	629	
43/00				643L	
A61K 31/435			31/435		
// (A61K 31/435					

Examination: Not yet requested No. of claims: 3 OL (total 7 pages) Continued on the final page

(21) Application No.: H10-324778

(22) Application date: November 16, 1998

(71) Applicant 000002819
Taisho Pharmaceutical Co., Ltd.
3-24-1 Takada, Toshima-ku, Tokyo

(72) Inventor Eiichiro Manabe
C/O Taisho Pharmaceutical Co., Ltd.
3-24-1 Takada, Toshima-ku, Tokyo

(74) Agent 100074114
Tomizo Kitakawa, Patent Attorney

F term (reference) 4C086 AA01 AA02 BC15 BC21 BC90 MA02 MA04 MA63 NA11 ZA08 ZA94

(54) **Title of the invention:** External-use composition

(57) **Abstract**

Issue: To provide an external-use composition that has high therapeutic effects on stiff shoulders and low-back pain.

Means for Resolution: An external-use composition that combines (A) at least one of any of an anti-inflammatory analgesic from among an anthranilic acid type, phenylacetic acid type, indole type, propionic acid type, pyrazolone type, benzothiazine type, and sulfonamide type and (B) eperisone or tolperisone or their salts.

Claims

Claim 1: An external-use composition that combines (A) at least one of any of an anti-inflammatory analgesic from among an anthranilic acid type, phenylacetic acid type, indole type, propionic acid type, pyrazolone type, benzothiazine type, and sulfonamide type and (B) eperisone or tolperisone or their salts.

Claim 2: The external-use composition noted in Claim 1 in which the anti-inflammatory analgesic of (A) is indomethacin.

Claim 3: The external-use composition noted in Claim 1 or Claim 2 in which with respect to 1 weight part of the anti-inflammatory analgesic, the combined amount of eperisone or tolperisone or their salts is 0.1–10 weight parts.

Detailed Explanation of the Invention

0001

Industrial Field of Application: This invention relates to an external-use compound that has high therapeutic value for stiff shoulders and low-back pain.

0002

Prior Art: A variety of anti-inflammatory analgesics are used for external treatment of stiff shoulders and low-back pain. Recently, external agents that combine anti-inflammatory analgesics such as anthranilic acid types, phenylacetic acid types, indole types, propionic acid types, pyrazolone types, benzothiazine types, and sulfonamide typesalong with a so-called stimulating anti-inflammatory analgesics such as salicylic acid and methyl salicylate, which have been widely used to date, have garnered attention and these are said to be transdermal absorption-type anti-inflammatory analgesics and among those, transdermal absorption-type anti-inflammatory analgesics that combine indomethacin, ketoprofen, flurbiprofen, fenbufen, piroxicam, and others have been developed.

0003: On the other hand, eperisone or tolperisone or their salts are known as agents that improve various symptoms due to spastic paralysis and muscle tonus conditions resulting from disorders such as shoulder-arm-neck syndrome, frozen shoulder, and low-back pain. Examinations have been made on transdermal administration as well, and combinations of fatty acid monoglycerides with carbon numbers of 8–12 and/or lactic acid esters of aliphatic alcohols with carbon numbers of 12–18 have been disclosed as bases to make satisfactory the transdermal permeability of eperisone and tolperisone or their salts (Patent Disclosure 1-52716).

0004

Problems the Invention is to Resolve: The purpose of this invention is to provide an external-use composition with high therapeutic efficacy for shoulder and low-back pain.

0005

Means for Resolving the Problems: On the basis of repeated research on the development of external-use compounds to increase the therapeutic effects on shoulder stiffness and low-back pain, the inventors of this invention achieved its perfection by discovering that when eperisone or tolperisone or their salts are mixed into anti-inflammatory analgesics, the eperisone or tolperisone or their salts increase the skin permeability of the anti-inflammatory analgesics.

0006: Specifically, this invention relates to an external-use composition that combines (A) at least one of any of anti-inflammatory analgesic from among anthranilic acid types, phenylacetic acid types, indole types, propionic acid types, pyrazolone types, benzothiazine types, and sulfonamide types and (B) eperisone or tolperisone, or their salts.

0007

Applied Form of the Invention: For the anti-inflammatory analgesic of this invention, possibilities include anthranilic acid types such as fenamic acid, phenylacetic acid types such as diclofenac and fenbufen, indole types such as indomethacin, propionic acid types such as ketoprofen and flurbiprofen, pyrazolone types such as phenylbutazone, benzothiazine types such as piroxicam, and sulfonamide types such as nimesulide. Among those, idomethacin is particularly desirable.

0008: In this invention, regarding the amount of the anti-inflammatory analgesic to be combined, in a composition (or in a stock solution in the case of an aerosol or in a paste in the case of an a plaster), the amount is preferably 0.1–5 weight % and in the case in which the anti-inflammatory analgesic is indomethacin, in particular, 0.3–3 weight % is desirable. If the amount of the anti-inflammatory analgesic to be mixed in is under 0.1 weight %, there are concerns that the anti-inflammatory analgesic effects of the composition will not be sufficiently demonstrated. In addition, if they are combined at greater than 5 weight %, the anti-inflammatory analgesic, particularly in the case of indomethacin, will demonstrate an increase in the precipitation amount of crystals due to solubility and, for example, there are concerns with plaster agents that their adhesive properties will decline and that there will be other adverse reactions and so problems arise at the time of formulation and in terms of adverse reactions.

0009: In this invention, regarding the amount of eperisone or tolperisone or their salts to be combined, in a composition (or in a stock solution in the case of an aerosol or in a paste in the case of a plaster), the amount is

preferably 0.1–10 weight % and more preferably, 0.3–5 weight % is desirable. If the combined amount of the substance is under 0.1 weight %, there are concerns that the transdermal absorption promoting effects will not be sufficiently demonstrated. In addition, when the combination is in excess of 10 weight %, there are concerns about adverse reactions and problems may arise at the time of formulation or in adverse reactions.

0010: In this invention, the combination ratio of eperisone or tolperisone or their salts with respect to the anti-inflammatory analgesic is intimately related to the transdermal absorption promoting action and is important from the perspective of formula design. That combination ratio is preferably 0.1–10 weight parts with respect to 1 weight part of anti-inflammatory analgesic. When this combination ratio is under 0.1 weight parts, there are concerns that the transdermal absorption promoting effects will not be sufficiently demonstrated. In addition, when the combination exceeds 10 weight parts, the balance of the formulation breaks down and there are formulating difficulties. In particular, in the case in which the anti-inflammatory analgesic is indomethacin, 0.1–5 weight parts with respect to 1 weight part of indomethacin is preferable.

0011: the pH of the external-use composition of this invention is preferably in the range of pH 3.5–7.0 from the standpoint of the stability of the drugs that have been combined and the range of pH 4.0–6.5 is further preferable. In addition, the external-use composition of this invention can be used in a dosage form that is typically used for an external agent, an a liquid agent, cream agent, ointment agent, gel agent, plaster agent, and an aerosol agent can be noted, and these can be manufactured according to an ordinary method described in the Japanese Pharmacopoeia or the like.

0012: The external-use composition of this invention has as base ingredients water and lower alcohols (such as methanol, ethanol, denatured ethanol, and isopropyl alcohol) and solubilizing agents, surfactants, emulsion stabilizers, and gelling agents can also be suitably used. In addition, perfumes and pigments may also be combined to the extent that they do not harm the effects of this invention.

0013: Furthermore, based on the usage objective of the external composition of this invention, a vasodilator, a corticosteroid, keratolytic agent, moisturizer, antiseptic agent, antioxidant, or cooling agent can be combined.

0014

Effects of the Invention: Through this invention, it is possible to provide an external-use composition with high therapeutic effects on stiff shoulders and low-back pain.

0015

Working Examples: Following we show working examples and test cases and provide a further detailed explanation of this invention.

0016

Working Example 1 (external-use liquid agent)

(Ingredients)	(Amount W/V%)
Indomethacin	1.0
Eperisone hydrochloride	2.0
Diisopropyl adipate	5.0
Isopropyl myristate	3.0
Glycerine	2.0
Polyoxyethylene alkyl ether	3.0
Denatured ethanol	45.0
Distilled water	Total 100 ml

The above-noted ingredients were agitated and a uniformly dissolved external-use liquid agent was obtained.

0017

Working Example 2 (cream agent)

(Ingredients)	(Amount W%)
Indomethacin	1.0
Eperisone hydrochloride	2.0
Medium chain triglycerides	20.0
Diisopropyl adipate	5.0
Propylene glycol	12.0
Polyoxyethylene sorbitan monostearate	6.0
Sorbitan monostearate	3.0
Glycerine monostearate	8.0
Distilled water	Total 100 g

A cream agent was prepared through a common method for cream agent manufacture, using the above-noted ingredients.

0018

Working Example 3 (gel agent)

(Ingredients)	(Amount W%)
Indomethacin	0.5
Eperisone hydrochloride	1.0
Polyethylene glycol monostearate	5.0
Diisopropyl adipate	3.0
1,3-butylene glycol	8.0
Polyvinylpyrrolidone	0.5
Carboxyvinyl polymer	1.5
Diisopropanolamine	Suitable amount
Denatured ethanol	30.0
Distilled water	Total 100 g

A gel agent was prepared according to a common method for gel agent manufacture, using the above-noted ingredients.

0019

Working Example 4 (plaster agent)

(Ingredients)	(Amount W%)
Indomethacin	0.5
Eperisone hydrochloride	1.0
Polyoxyethylene sorbitan monooleate	1.0
Propylene glycol	5.0
Polyacrylic acid	7.0
Sodium polyacrylate	6.0
Anhydrous silicic acid	1.0
Tartaric acid	0.5
Aluminum glycinate	Suitable amount
Aluminum hydroxide	Suitable amount
Distilled water	Total 100 g

A plaster agent was prepared according to a common method for plaster agent manufacture, using the above-noted ingredients.

0020

Working Example 5 (aerosol agent)

(Ingredients)	(Amount W%)
Indomethacin	1.4
Eperisone hydrochloride	2.0
Polyoxyethylene sorbitan tristearate	1.2
Diisopropyl adipate	2.0
1,3-butylene glycol	1.2
Ethanol	20.0
Distilled water	12.2
Isopentane	10.0
Liquefied petroleum gas	3.0
Dimethyl ether	47.0

An aerosol agent was prepared according to a common method for aerosol plaster agent manufacture, using the above-noted ingredients.

0021

Working Example 6 (plaster agent)

(Ingredients)	(Amount W%)
Ketoprofen	0.5
Eperisone hydrochloride	2.0
Polyoxyethylene sorbitan monooleate	1.0
Propyleneglycol	5.0
Polyacrylic acid	7.0
Sodium polyacrylate	6.0
Anhydrous silicic acid	1.0

Tartaric acid	0.5
Aluminum glycinate	Suitable amount
Aluminum hydroxide	Suitable amount
Distilled water	Total 100 g

A plaster agent was prepared according to a common method for plaster agent manufacture, using the above-noted ingredients.

0022

Working Example 7 (plaster agent)

(Ingredients)	(Amount W%)
Flurbiprofen	0.5
Eperisone hydrochloride	2.0
Polyoxyethylene sorbitan monooleate	1.0
Propylene glycol	5.0
Polyacrylic acid	7.0
Sodium polyacrylate	6.0
Anhydrous silicic acid	1.0
Tartaric acid	0.5
Aluminum glycinate	Suitable amount
Aluminum hydroxide	Suitable amount
Distilled water	Total 100 g

A plaster agent was prepared according to a common method for plaster agent manufacture, using the above-noted ingredients.

0023

Working Example 8 (plaster agent)

(Ingredients)	(Amount W%)
Fenbufen	0.5
Eperisone hydrochloride	3.0
Polyoxyethylene sorbitan monooleate	1.0
Propylene glycol	5.0
Polyacrylic acid	7.0
Sodium polyacrylate	6.0
Anhydrous silicic acid	1.0
Tartaric acid	0.5
Aluminum glycinate	Suitable amount
Aluminum hydroxide	Suitable amount
Distilled water	Total 100 g

A plaster agent was prepared according to a common method for plaster agent manufacture, using the above-noted ingredients.

0024

Working Example 9 (plaster agent)

(Ingredients)	(Amount W%)
Piroxicam	0.5
Eperisone hydrochloride	2.0
Polyoxyethylene sorbitan monooleate	1.0
Propylene glycol	5.0
Polyacrylic acid	7.0
Sodium polyacrylate	6.0
Anhydrous silicic acid	1.0
Tartaric acid	0.5
Aluminum glycinate	Suitable amount
Aluminum hydroxide	Suitable amount
Distilled water	Total 100 g

A plaster agent was prepared according to a common method for plaster agent manufacture, using the above-noted ingredients.

0025: Working Example 10

An external-use liquid agent was prepared according to the same method as Working Example 1, using a formula in which the eperisone hydrochloride of Working Example 1 was changed to tolperisone hydrochloride at 2.0 W/V%.

0026: Working Example 11

A plaster agent was prepared according to the same method as Working Example 4, using a formula in which the eperisone hydrochloride of Working Example 4 was changed to tolperisone hydrochloride at 1.0 W%.

0027: Working Example 12

A plaster agent was prepared according to the same method as Working Example 5, using a formula in which the eperisone hydrochloride of Working Example 5 was changed to tolperisone hydrochloride at 2.0 W%.

0028: Working Example 13

A plaster agent was prepared according to the same method as Working Example 6, using a formula in which the eperisone hydrochloride of Working Example 6 was changed to tolperisone hydrochloride at 1.0 W%.

0029: Working Example 14

A plaster agent was prepared according to the same method as Working Example 7, using a formula in which the eperisone hydrochloride of Working Example 7 was changed to tolperisone hydrochloride at 1.0 W%.

0030: Working Example 15

A plaster agent was prepared according to the same method as Working Example 8, using a formula in which the eperisone hydrochloride of Working Example 8 was changed to tolperisone hydrochloride at 1.0 W%.

0031: Working Example 16

A plaster agent was prepared according to the same method as Working Example 9, using a formula in which the eperisone hydrochloride of Working Example 9 was changed to tolperisone hydrochloride at 1.0 W%.

0032: Comparison Example 1

A comparison liquid agent was prepared according to the same method as Working Example 1, using a formula in which the eperisone hydrochloride of Working Example 1 was eliminated and the full amount was adjusted with distilled water.

0033: Comparison Example 2

A comparison liquid agent was prepared according to the same method as Working Example 1, using a formula in which the indomethacin of Working Example 1 was eliminated and the full amount was adjusted with distilled water.

0034: Comparison Example 3

A comparison liquid agent was prepared according to the same method as Working Example 1, using a formula in which the indomethacin and eperisone hydrochloride of Working Example 1 was eliminated and the full amount was adjusted with distilled water.

0035: Test 1 (Drug substance skin permeation test) (Eiichiro Manabe et al., Pharmacy, 58 (1), 10–16 (1998))

Abdominal area skin of male hairless rats (7 weeks old) was isolated with the animals under sodium pentobarbital anesthesia (50 mg/kg i.p.). The isolated skin was inserted into a 2-chamber horizontal diffusion cell with an effective diffusion area of 0.95 cm^2, maintained in advance at 37°C. To the donor-side (stratum corneum) chamber, 2.5 mL of a test sample (Working Example 1, Comparison Example 1) was added. To the receiver-side (dermis) chamber, 2.5 mL of a 1/15M isotonic phosphate buffer solution was added and over time, a fixed amount of sample solution was taken from the receiver side and at those times, the same amount of buffer solution was added and the volume was maintained constant. The amount of indomethacin in the sample collected was measured and the skin permeability of the drug substance was investigated. The results are shown in Fig. 1.

0036: As is evident from Fig. 1, eperisone hydrochloride increased the skin penetration amount of indomethacin.

0037: Test 2 (shoulder stiffness improvement test)

An efficacy questionnaire test was performed on 10 patients who complained of shoulder stiffness using the formulations obtained in Working Example 1 and those obtained in Comparison Examples 1–3. Regarding dose and administration method, 4 times a day was taken as the limit and a suitable amount was applied to the affected area. At the time of the completion of the administration, the degree of improvement in shoulder stiffness symptoms was evaluated in comparison to the condition at the start of administration according to the following five grades: clear improvement, moderate improvement, mild improvement, no change, and worsening. Results demonstrated marked efficacy, as shown in Table 1.

0038

Table 1

Tested substance	Number of persons				
	Clear improvement	Moderate improvement	Mild improvement	No change	Worsening
Working Example 1	3	5	2	0	0
Comparison Example 1	0	2	5	2	1
Comparison Example 2	0	3	3	4	0
Comparison Example 3	0	0	2	5	3

Brief Explanation of the Drawings

Fig. 1 shows changes over time in the amount of indomethacin skin penetration.

Fig. 1

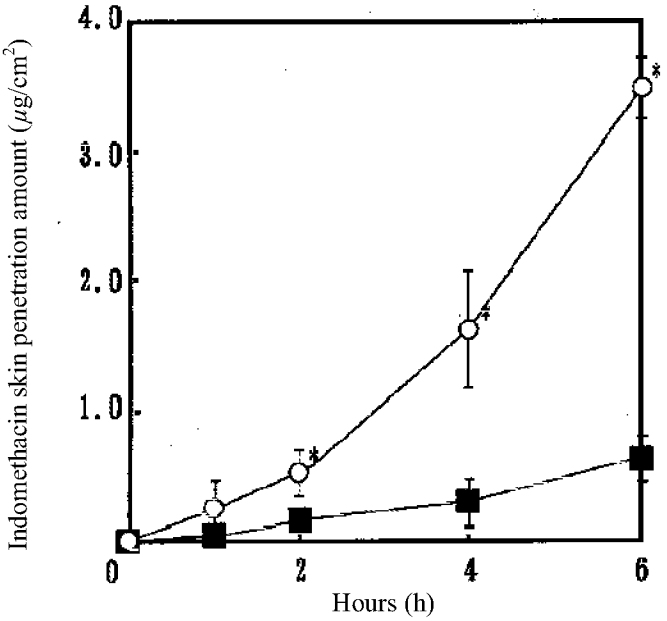

Fig. 1

Changes over time in indomethacin skin penetration amount

○: Working Example 1, ■: Comparison Example 1.

Each value shows the mean values of 6 tests and the standard deviation (S.D.).

* indicates that both are significantly different with the hazard ratio (P) at under 0.05.

Continued from the front page

(51) Int. Cl.[7]	ID Code	FI	(reference)
A61K 31:40)			